Osteoid metaplasia with functioning marrow is a rare pathological process in arterial calcifications, associated to the asymptomatic development of atherosclerotic plaques. Objective: To describe morphological aspects of bone metaplasia in arterial calcifications and its pathogenesis in two cases. Macroscopic examination of iliac arteries was performed and fragments of approximately 2 cm of the right and left iliac arteries were collected for microscopic analysis of atherosclerosis. These fragments were processed histologically and stained with hematoxylin and eosin (HE). A pronounced atherosclerosis, characterized by diffuse atheroma plaques and foci of calcifications, was evidenced. In both cases, in intima layer of atherosclerotic plaque in right iliac artery, a dilatation, and the presence of bone metaplasia with bone trabeculae, calcifications, and functioning bone marrow with red blood cells and megakaryocytes were observed. Due to the rarity of this lesion, its description allows better characterization of morphological data and pathogenesis.

Keywords: Autopsy, Bone marrow, Calciosis, Iliac artery

INTRODUCTION

Progression of atherosclerotic lesions leads to accumulation of extracellular lipids and calcium, with partial or total obstruction of vascular lumen [1]. The prevalence of arterial calcification in atherosclerotic lesions is 90%, considered as an independent risk factor for cardiovascular mortality [2, 3].

Arterial calcification interferes with atherosclerotic plaque stability and may lead to its rupture. Microcalcifications increase the risk of rupture [4, 5], but lesions with high calcium volume are generally more stable [6, 7]. Calcifications also interfere with endovascular repair during surgical procedure, making it difficult to repair vessels and perform arterial anastomoses [8, 9].

Rarely, bone tissue can be formed in atheromatous lesions, characterized by osteoid matrix, bone cells, osteoclasts, and regulatory bone cytokines [7]. This formation, in carotid lesions, is a process known as osteoid metaplasia and is associated with asymptomatic development of atherosclerotic plaques [7]. The formation of bone tissue with functioning bone marrow in an arterial calcification is a poorly elucidated pathological process in scientific literature [10].
Autopsy material is very interesting for research. Therefore, this study aims to describe morphological aspects and pathogenesis of bone metaplasia in arterial calcifications.

CASE SERIES

Methods

The present study was approved by the Research Ethics Committee of Federal University of Triângulo Mineiro, according to the certificate of presentation for ethical appreciation (CAAE): 56931816.4.0000.5154.

Pathology examination

The anatomopathological examination was performed in HC-UFTM by necropsy in two white patients, the patient 1 was 82 years old, female, with body weight of 35 kg and height of 140 cm, leading to a body mass index of 17.9 kg/m², characteristics of marked malnutrition. She presented anasarca, probable osteoporosis, sternal and rib friability, and surgical scar due to correction of right femoral neck fracture. Internal examination revealed severe atherosclerotic arteriosclerosis in aorta and its main branches, which, in association with a localized compression of the large intestinal mucosa by a stony fecal mass, were probably responsible for ischemic colitis and hemorrhagic infarction in colon. There was also an ulcerated gastric adenocarcinoma, with raised borders and an approximate diameter of 7 cm, associated with hemorrhage.

The patient 2 was female, 92 years old, body weight was 53 kg, and the height was 163 cm, with a body mass index of 19.9 kg/m², characterizing malnutrition. On internal examination, presented bilateral acute bronchopneumonia, especially in lower and posterior lobes, marked atherosclerosis in aorta and its main branches, probable ischemic colitis, senile hypotrophy of pancreas, spleen, ovary, and thyroid. There was also a hiatal hernia through which gastric fundus was insinuated.

Material preparation

Fragments of approximately 2 cm of right and left iliac arteries were collected. These fragments were processed histologically by fixation in 10% formaldehyde, dehydration in alcohols with increasing concentrations (70–100%), diaphanization in xylol and paraffin embedding. Then, serial 4-μm thick sections were performed and slides were obtained for histological analysis.

Slides were stained with HE for evaluation under light microscopy with a 20× objective and a final magnification of 1200×.

RESULTS

In arterial macroscopic analysis, marked atherosclerosis was evidenced in both cases, with diffuse atheroma plaques and foci of calcifications.

In microscopic analysis, extensive atherosclerotic lesions in the right and left iliac arteries with inflammatory cells and calcification were seen. In right iliac artery in both cases, a bone metaplasia was observed, with trabecular bone, calcifications, functioning bone marrow (Figure 1) with red blood cells and megakaryocytes on the atherosclerotic plaque in the intima layer, resulting in local bulging.

DISCUSSION

Anatomopathological examination in both cases showed marked atherosclerosis of aorta and its main branches. Microscopic analysis of the right and left iliac arteries showed atherosclerotic plaque, with bone metaplasia associated with calcification in the intimal layer of the right iliac artery in both cases.

Heterotopic bone formation has been shown to be closely related to calcification process and its presence has been reported particularly in the aortic valve, mitral valve calcified ring (annular calcification), and rarely in arterial atherosclerotic plaques [6, 12, 13]. The pathogenesis is controversial, with studies advocating the transformation of connective tissue into bone, and others arguing that bone formation occurs due to attachment to cartilage, bone, bone embryonic matrix, or cartilage [14].

It was recognized that there may be an active process of bone formation in advanced lesions [15], demonstrated by the expression of bone metabolizing proteins and the presence of bone metaplasia. This metaplasia is observed in approximately 15.6% of resected aortic valves, characterizing a late histological finding in the progression of aortic sclerosis to aortic stenosis [16], and its clinical significance is unknown.

The pathogenesis underlying bone metaplasia in aortic valves with stenosis is unclear, especially regarding the origin metaplastic cell. The source may be native

Figure 1: Microscopic analysis of right iliac arteries, indicating arterial dilation with bone metaplasia (arrow) and functioning bone marrow formation (arrowhead) (HE 1600×). (A) Patient 1, (B) Patient 2.
differentiated valvar interstitial cells and/or circulating mesenchymal stem cells. These native valvar interstitial cells are a heterogeneous cellular group that compose the majority of aortic valve cellular population and are responsible for maintaining local homeostasis. They can turn into an osteogenic phenotype when exposed to a variety of signs [17]. There is also evidence that stem cells contribute to heterotic ossification in atherosclerosis [18, 19], and it has been shown that hematopoietic cells derived from bone marrow can populate atherosclerotic lesion [20, 21].

In aortic valve stenosis, several bone-associated proteins are expressed as bone sialoprotein and bone morphogenetic protein 2, indicating that calcification may be an actively regulated process [22]. The occurrences of bone metaplasia or functional bone marrow in arterial calcification are rare pathological findings and may be asymptomatic. Surgical repair may be a strategy to prevent possible lethal complications [23].

It was believed that bone formation occurred only in aorta and cardiac vessels, but it was shown that vessels from extremities might also be involved, including places outside the vessels [24]. A necropsy study described a patient who died due to generalized infection, who had aortic arterial thickening due to atherosclerosis and two portions of bone formation were observed in the intimal layer. In a similar study, bone formation with red, white, and giant cells was found in the sclerotic portion of aorta [24].

Recent studies have shown the presence of pericytes involved in calcification process, as well as other factors that regulate bone remodeling. Another substance involved in the process arterial bone formation is osteoprotegerin (OPG), with high rates of expression in arterial lesions with metaplasia, as it inhibits osteoclast activation, favoring the process of bone formation. Both substances involved are recruited for osteoclast activation, favoring the process of bone formation due to inflammatory stress, causing an attempt to defend aggression by inducing local mineral formation. Therefore, as atherosclerotic lesions evolve, it increases the chances of developing bone metaplasia [7].

The occurrence of severe atherosclerosis associated with bone metaplasia probably contributed to mesenteric circulation acute changes found in the first patient, considered an emergency, as the most prevalent risk factors for this disease are atherosclerosis of aorta and its branches, arterial stenosis, and different types of heart failure [11, 24].

**CONCLUSION**

The morphological description of bone metaplasia in atheromatous plaques is relevant to characterize new data about the disease and to emphasize the importance of considering calcium deposition, atherosclerotic disease progression, and the presence of substances that favor its formation to avoid complications, such as plaque rupture and arterial stenosis.

**REFERENCES**


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